REMARKS

Claims 13-15 are all the claims pending in the application; each of the claims has been rejected.

The amendment to claims 13 and 14 to recite that step C is performed using a different, non-overlapping region of the selected DNA molecule finds support in the example set forth in the application, directed to the use of different, non-overlapping regions of a selected DNA molecule (see Figure 1).

No new matter has been added. Entry of the Amendment is respectfully requested.

I. Rejection of Claims Under 35 U.S.C. §112

A. At page 2 of the Office Action, the rejection of claims 13-15 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, has been maintained. The Examiner notes that this is a new matter rejection.

The Examiner is interpreting step C in claims 13 and 14 as encompassing two different methods. The first method encompasses repeating steps A and B on a different region of the selected DNA molecule (e.g., nucleotides 200-300 versus nucleotides 400-500 on a selected DNA molecule). The second method encompasses repeating steps A and B on a different portion of the same region of the selected DNA molecule (e.g., nucleotides 200-300 versus nucleotides 200-220). The Examiner contends that the specification does not provide support for the latter method, that is, selecting a region for testing and then repeating the testing using the same region but a different portion of that region.

In order to more clearly recite that which Applicants regard as their invention, included herewith is an amendment to claims 13 and 14 to more clearly recite that step C is performed using a different, non-overlapping region of the selected DNA molecule.

In view of the amendment to the claims, the claims are fully supported by the specification and Applicants respectfully request reconsideration and withdrawal of this rejection.

B. At page 5 of the Office Action, the rejection of claims 13-15 under 35 U.S.C. §112, second paragraph, as being indefinite, has been maintained.

(1) The Examiner states that the phrase "that is different from the selected portion of (B)" does not clearly identify whether the claimed methods require one to select a region to be tested and then repeat the method on an entirely different region, or if the method requires one to select a region to be tested and then repeat the method using the same region but a different portion of that region.

As discussed above, claims 13 and 14 have been amended to more clearly recite the invention. As the claims now recite that steps A and B are repeated on a selected portion of the selected DNA molecule "that is different from and non-overlapping with" the portion selected in step B, it is clear that the claimed method requires one to select a region to be tested and then repeat the method on an entirely different region. The amendment also makes clear that the claimed method does not encompass selection of a region to be tested and then repeating the method using the same region but a different portion of that region.

(2) The Examiner states that the term "corresponding" in the phrase "corresponding to a selected portion of" is not an art recognized term to describe the relationship between two nucleic acid sequences or two amino acid sequences. Specifically, the Examiner contends that it would not be clear as to whether a corresponding nucleic acid refers to a nucleic acid residue at the same position or to one which is at a nearby position, or whether it refers to a similar nucleic acid residue or the same nucleic acid residue at any position. The Examiner notes that while Applicants argue that the term is recognized in the art, no evidence in support of this position has been provided.

While Applicants understand the term "corresponding" to be an art recognized term, in order to advance prosecution of this application included herewith is an amendment to claims 13 and 14 such that the claims now recite that the RNA transcript is "encoded by" the DNA molecule.

(3) The Examiner states that the phrase "a selected portion of" is not clearly defined in the specification and that there is no art recognized definition of this phrase. Specifically, the

Examiner reasons that it would be unclear as to whether the phrase refers to any portion of any DNA sequence that has been selected by virtue of amplifying it or a portion of a specific DNA sequence.

Applicants respectfully traverse the Examiner's position and assert that the phrase "a selected portion of" is clear, and that the phrase would be well understood by one of ordinary skill in the art reading the pending claims. Upon selecting a DNA molecule, one practicing the recited methods would then select a portion of the selected DNA molecule for which to screen the RNA transcripts. For example, if the selected DNA molecule is 1000 nucleotides in length, and one wished to determine whether the portion of the DNA molecule consisting of nucleotides 200-300 encodes a gene expression region, the portion consisting of nucleotides 200-300 would be the "selected portion of" the selected DNA molecule.

In view of the comments above concerning each of the three issues raised in this rejection, and in view of the amendments to the claims, Applicants respectfully assert that the claims are definite as written and request reconsideration and withdrawal of this rejection.

II. Rejection of Claims Under 35 U.S.C. §103

A. At page 8 of the Office Action, the rejection of claim 13 under 35 U.S.C. §103(a) as being unpatentable over Davey et al. (U.S. patent No. 5,409,818) in view of Cao (U.S. Patent No. 6,582,906), has been maintained.

At pages 9-11 of the Office Action, the Examiner indicates the location of support in Davey et al. for each element of pending claim 13. The Examiner admits that Davey et al. does not teach repeating the method on a different portion of the selected DNA molecule.

The Examiner states that Cao teaches a method for analyzing gene expression in which the method steps are repeated using a different portion of a selected DNA molecule. The Examiner explains that Cao teaches that the method is repeated once or multiple times, that each round of the method for amplifying a population of nucleic acids involves producing multiple copies of sense RNA from double-stranded DNA, and that each time the method is repeated the starting population of RNA is different because the cDNA is fragmented and therefore a population of different double-stranded DNA sequences is produced.

In response to the traversing arguments set forth in the Amendment filed August 17, 2006, the Examiner states that because the cDNA is fragmented in the method recited in the instant application, each fragment is being interpreted as a different region. The Examiner further states that the skilled artisan would have been motivated to combine the teachings of the two patents in order to achieve the benefits of Cao, namely, of providing a method which overcomes having to analyze long templates for gene expression which can be difficult and less efficient due to interference from secondary and tertiary structures in the template.

Applicants maintain their traversal of the instant rejection for the reasons of record, and for the additional reasons set forth below. In particular, Applicants respectfully assert that the Examiner has not established a *prima facie* showing of obviousness.

Applicants first note that Cao recognizes that when conducting an amplification reaction, there is a bias towards the amplification of shorter nucleic acid templates in a sample (col. 1, lines 48-50). As a result, the ratio of amplification products is skewed towards the smaller templates in the sample. Cao suggests that this problem is due in part to the greater likelihood of a polymerase completing the copying event of a shorter template verses a longer template. Circumstances such as (i) interference due to secondary and tertiary structures in longer templates, (ii) lack of annealing of primers to incomplete amplification products, and (iii) lack of sufficient denaturation of longer templates are thought to be reasons why the polymerase is less successful in copying longer templates. Cao discloses a method of addressing the problem by synthesizing ssDNA from a population of RNA, fragmenting the ssDNA to produce a population of short ssDNA templates, producing dsDNA from the short ssDNA templates, and producing sense RNA from the dsDNA. Thus, the amplification takes place using ssDNA templates that are each of an approximately equivalent size. As a result, there is a proportional amplification of the nucleic acid molecules (which is the title of this patent). Cao notes that the method can be repeated more than once (col. 3, lines 4-6).

In contrast to the Examiner's position that Cao "teaches a method used to analyze gene expression," it is clear from the description of the patented method set forth above that the method of Cao is simply a method for the *proportional amplification* of nucleic acids, as

suggested by the title of Cao. Cao does not provide any teachings with regard to means for *analyzing the expression* of a gene.

Moreover, the Examiner has admitted that Davey et al. does not teach the repetition step recited in step C of claim 13. Applicants maintain their position that Cao also does not teach the repetition step C of claim 13.

In particular, step C of claim 13 requires that the amplification be repeated on a portion of the selected DNA molecule that is different from the selected portion amplified in the first round of amplification. The Examiner argues that each time the method of Cao is repeated, the starting population of RNA is different. Applicants note that the method of Cao begins with the synthesis of ssDNA from a population of RNAs (col. 6; claim 1). The ssDNA is then fragmented, dsDNA is made from the ssDNA fragments, and sense RNA is produced from the dsDNA. The Examiner argues that when the method is repeated, the RNA used in the second round of amplification (produced from the first round) is different from the RNA used in the first round of amplification. However, Applicants respectfully note that the RNA produced from the first round and used in the second round would necessarily be a portion of the RNA molecules used in the first round due to the fragmentation of the ssDNA. Therefore, the second round of amplification would be considered to be a different portion of the same region of the RNA molecule. As discussed above in section **I.A.**, claim 13 has been amended to make clear that step C is performed using a different, non-overlapping region of the selected DNA molecule. Accordingly, Cao does not teach each and every element of step C as amended.

Furthermore, there would have been no motivation to combine the teachings of Davey et al. and Cao. In particular, Davey et al. teaches a method of amplifying a specific nucleic acid sequence. Thus, one practicing the invention of Davey et al. starts with a small amount of a selected nucleic acid sequence, and obtains a larger quantity of the selected nucleic acid sequence by practicing the method of Davey et al. The skilled artisan would have no reason to repeat the method on a different, non-overlapping portion of the selected nucleic acid molecule. Once the amplification process has been completed, the method of Davey et al. is complete.

While it is conceivable that the skilled artisan could selected a second group of primers and repeat the amplification process on the selected nucleic acid molecule, there would be no reason for doing so. While the Examiner suggests that the skilled artisan would include the steps of Cao to overcome the difficulties and low efficiencies of analyzing long templates for gene expression, the Examiner has not cited to any passage of Davey et al. that suggests such problems, or evidence that the skilled artisan would expect such problems when using the method of Davey et al. Indeed, neither the method of Davey et al. nor the method of Cao is a method of analyzing gene expression. Both disclosures are simply methods for amplifying nucleic acid molecules.

Moreover, the method of Davey et al. is used to increase the quantity of a specific nucleic acid sequence in a sample, thereby increasing the likelihood that a probe will detect a selected nucleic acid sequence in the sample (see Background section). If the selected nucleic acid sequence of Davey et al. was fragmented, through the use of the method of Cao, there is no indication that the probe would maintain its ability to detect the selected nucleic acid in the sample. Indeed, as the fragmentation of the nucleic acid is non-specific, the skilled artisan might readily expect that the region of complementarity with the probe might be destroyed upon fragmentation. As such, not only would the skilled artisan lack motivation to combine the teachings of these two patents, the skilled artisan would not have had a reasonable expectation of success in combining the teachings of these two patents.

As the Examiner has thus not established a *prima facie* showing of obviousness, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. At page 13 of the Office Action, the rejection of claims 14 and 15 under 35 U.S.C. § 103(a) as being unpatentable over Davey et al. in view of Cao and in further view of Wittwer et al. (U.S. Patent No. 6,503,720 B2) has been maintained.

The Examiner relies on Davey et al. and Cao for the reasons stated above. The Examiner admits that neither reference teaches the detection of the amplification product using an oligonucleotide probe labeled with an intercalating fluorescence dye or one having a differential fluorescence characteristic.

The Examiner states that Wittwer et al. teaches such an intercalating probe in the teaching of PCR amplification and subsequent SYBR green detection, and further teaches an intercalating fluorescence dye having a fluorescence character in the teaching of the Taq Man principle to detect amplification. The Examiner concludes that it would have been *prima facie* obvious to a skilled artisan to combine the method of Davey et al and Cao, with Wittwer et al.

In response to the arguments in the Amendment filed August 17, 2006, that Wittwer et al. does not cure the deficiency of Davey et al. and Cao, the Examiner merely provides further comments with regard to the teachings of Wittwer et al. The Examiner does not indicate how Wittwer et al. cures the lack of teaching in Davey et al. and Cao of repeating the amplification step on a different portion of the same selected DNA molecule.

Applicants maintain their traversal of the instant rejection for the reasons of record. In particular, neither Davey et al. nor Cao teaches repetition of the amplification step on a different, non-overlapping portion of the same selected DNA molecule, and that Wittwer et al. does not cure the defect.

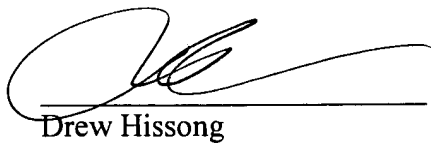
As the Examiner has thus not established a *prima facie* showing of obviousness, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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